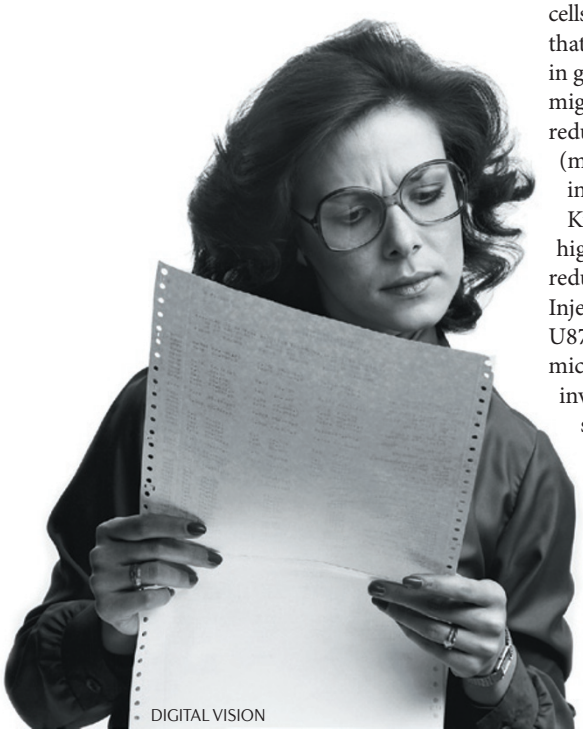
MICRORNAS

Editing changes the meaning

> “miR-376a* that cannot be edited … increased *in vitro* migration and invasion”

Lower levels of adenosine-to-inosine (A-to-I) editing of mRNAs have been observed in some cancers, particularly in high-grade gliomas. The microRNA (miRNA) cluster miR-376 is subject to A-to-I editing in the brain; however, whether miR-376 editing is disrupted in gliomas, and whether this has relevant functional consequences is not known.

Shu Wang and colleagues identified reduced editing of miR-376a* (one of five mature miRNAs produced by the cluster) in high-grade human glioma samples, and this correlated with a higher tumour volume on patient magnetic resonance imaging scans. They also showed that miR-376a* editing occurs in glioma cell lines, and used U87 cells to further characterize the biological effects of miR-376a* editing. U87 cells that were selected for metastatic activity by tail-vein injections and reculturing *in vitro* had higher levels of unedited miR-376a* than parental (less metastatic) U87 cells. Stable expression of miR-376a* that cannot be edited (miR-376a*A) in glioma cell lines increased *in vitro* migration and invasion, and this was reduced by a stably edited miR-376a* (miR-376a*G; guanosine mimics inosine functionally in miRNAs).



DIGITAL VISION

Knockdown of miR-376a* in the highly metastatic U87 cells also reduced invasion and migration. Injection of miR-376a*A-expressing U87 cells into the brains of nude mice led to the formation of more invasive tumours and reduced survival time of the animals, compared with tumours formed from miR-376a*G-expressing cells.

The authors used microarray profiling to examine which gene targets are modified by edited and unedited miR-376a*, and identified the RAS family member *RAP2A* as a potential miR-376a*A target and autocrine motility factor receptor (*AMFR*) as a potential miR-376a*G target. They confirmed the specificity of each miRNA for its respective target, and showed that unedited miR-376a*A, but not miR-376a*G, reduced the levels of *RAP2A* mRNA and protein in U87 and SW1783 cells. Conversely, miR-376a*G, but not miR-376a*A, reduced the levels of *AMFR* mRNA and protein. Additional *in vitro* experiments showed that RAP2A or AMFR knockdown phenocopied the effects of miR-376a*A or miR-376a*G, respectively, on migration and invasion. Furthermore, RAP2A expression could rescue miR-376a*A-induced invasion, and AMFR expression increased invasion in miR-376a*G-expressing cells.

Unedited miR-376a* levels were inversely correlated with *RAP2A* mRNA levels and positively correlated with *AMFR* levels in human and mouse tumour samples. In patient data from publicly available databases, low *RAP2A* levels were observed in high-grade glioma and significantly correlated with reduced patient survival, suggesting that this miRNA editing and target alteration pathway could be relevant in human cancer.

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ORIGINAL RESEARCH PAPER Choudhury, Y. *et al.* Attenuated adenosine-to-inosine editing of microRNA-376a* promotes invasiveness of glioblastoma cells. *J. Clin. Invest.* **122**, 4059–4076 (2012)